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PTO/SB/05 (4/98)
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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))

Attorney Docket No.	CIMA 3.0-030 CONT II
First Inventor or Application Identifier	Pather
Title	Sublingual Buccal Effervescent
Express Mail Label No.	EL 479160807US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231

1. [x] * Fee Transmittal Form (e.g., PTO/SB/17) (Submit an original and a duplicate for fee processing)
2. [x] Specification [Total Pages 20] (preferred arrangement set forth below)
   - Descriptive title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings (if filed)
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
3. [ ] Drawing(s) (35 U.S.C. 113) [Total Sheets 0]
4. Oath or Declaration [Total Pages 2]
   a. [ ] Newly executed (original or copy)
   b. [x] Copy from a prior application (37 C.F.R. § 1.63(d)) (for continuation/divisional with Box 16 completed)
      i. [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).

*NOTE FOR ITEMS 1 & 13: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).

5. [ ] Microfiche Computer Program (Appendix)
6. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
   a. [ ] Computer Readable Copy
   b. [ ] Paper Copy (identical to computer copy)
   c. [ ] Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

7. [ ] Assignment Papers (cover sheet & document(s))
8. [ ] 37 C.F.R.§3.73(b) Statement (when there is an assignee) [ ] Power of Attorney
9. [ ] English Translation Document (if applicable)
10. [x] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copies of IDS Citations
11. [x] Preliminary Amendment
12. [x] Return Receipt Postcard (MPEP 503) (Should be specifically itemized)
13. [ ] * Small Entity Statement(s) (PTO/SB/09-12) [ ] Statement filed in prior application, Status still proper and desired
14. [ ] Certified Copy of Priority Document(s) (if foreign priority is claimed)
15. [ ] Other: ....

16. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below and in a preliminary amendment:

[XX] Continuation [ ] Divisional [ ] Continuation-in-part (CIP) of prior application No: 09 / 327,814

Prior application information: Examiner I. Ghali Group / Art Unit: 1615

For CONTINUATION or DIVISIONAL only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 4b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

17. CORRESPONDENCE ADDRESS

[ ] Customer Number or Bar Code Label 000530 (Insert Customer No. or Attach bar code label here) or [ ] Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Fax	

Name (Print/Type)	Jason I. Garbell	Registration No. (Attorney/Agent)	44,116
Signature	[signature]	Date	09/14/00

PTO/SB/17 (12/99)
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FEE TRANSMITTAL for FY 2000

Patent fees are subject to annual revision
Small Entity payments must be supported by a small entity statement, otherwise large entity fees must be paid See Forms PTO/SB/09-12. See 37 C F.R §§ 1.27 and 1 28.

TOTAL AMOUNT OF PAYMENT ($) 690.00

Complete if Known	
Application Number	
Filing Date	
First Named Inventor	Pather
Examiner Name	I. Ghali
Group / Art Unit	1615
Attorney Docket No.	CIMA 3.0-030 CONT II

METHOD OF PAYMENT (check one)

1. [X] The Commissioner is hereby authorized to charge indicated fees and credit any overpayments to:

Deposit Account Number: 12-1095

Deposit Account Name: Lerner, David et al.

[X] Charge Any Additional Fee Required Under 37 CFR §§ 1 16 and 1.17

2. [ ] **Payment Enclosed:** [ ] Check [ ] Money Order [ ] Other

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	690	201	345	Utility filing fee	690
106	310	206	155	Design filing fee	
107	480	207	240	Plant filing fee	
108	690	208	345	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) ($)690.00

2. EXTRA CLAIM FEES

		Extra Claims		Fee from below	Fee Paid
Total Claims	8	-20** = 0	X	18	= 0
Independent Claims	1	- 3** = 0	X	78	= 0
Multiple Dependent					= 0

**or number previously paid, if greater; For Reissues, see below

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	78	202	39	Independent claims in excess of 3
104	260	204	130	Multiple dependent claim, if not paid
109	78	209	39	** Reissue independent claims over original patent
110	18	210	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)0.00

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet.	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	380	216	190	Extension for reply within second month	
117	870	217	435	Extension for reply within third month	
118	1,360	218	680	Extension for reply within fourth month	
128	1,850	228	925	Extension for reply within fifth month	
119	300	219	150	Notice of Appeal	
120	300	220	150	Filing a brief in support of an appeal	
121	260	221	130	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,210	241	605	Petition to revive - unintentional	
142	1,210	242	605	Utility issue fee (or reissue)	
143	430	243	215	Design issue fee	
144	580	244	290	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	240	126	240	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	690	246	345	Filing a submission after final rejection (37 CFR § 1.129(a))	
149	690	249	345	For each additional invention to be examined (37 CFR § 1.129(b))	

Other fee (specify) _____

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($)

SUBMITTED BY				Complete (if applicable)	
Name (Print/Type)	Jason I. Garbell	Registration No. (Attorney/Agent)	44,116	Telephone	908 654 5000
Signature				Date	9/14/00

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Burden Hour Statement. This form is estimated to take 0 2 hours to complete. Time will vary depending upon the needs of the individual case Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231 DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

PATENT
CIMA 3.0-030 CONT II

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of Pather et al.	
Continuation of Prior Application No. 09/327,814	Group Art Unit: 1615 Examiner: I. Ghali
Filed: Herewith	Date: September 14, 2000
For: Sublingual Buccal Effervescent	

Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

After according a filing date to the above-identified 53(b) Continuation Application, please amend the application as follows:

IN THE SPECIFICATION

Please insert as the first line of the specification following the Cross Reference to Related Application:

--The present application is a continuation application of United States Patent Application No. 09/327,814 filed June 8, 1999, the benefit of which is claimed under 35 U.S.C. § 120.--

IN THE CLAIMS:

Please delete original claims 1-13 and add the following new claims:

14. A solid pharmaceutical dosage form adapted for direct oral administration across the oral mucosa comprising:

a pharmaceutically effective amount of an orally administerable medicament; wherein said orally administerable medicament is not substantially encompassed by or dispersed in a

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material that prevents absorption of said orally administerable medicament across the oral mucosa; and

at least one saliva activated effervescent agent present in an amount sufficient to increase absorption of said orally administerable medicament across the oral mucosa.

15. The solid pharmaceutical dosage form of claim 14 further comprising at least one pH adjusting substance.

16. The solid pharmaceutical dosage form of claim 14 further comprising a bioadhesive, wherein said bioadhesive increases the contact time between said dosage form and the oral mucosa.

17. The solid pharmaceutical dosage form of claim 14 further comprising a non-effervescent disintegration agent.

18. The solid pharmaceutical dosage form of claim 14 further comprising glidants, lubricants, binders, sweeteners, flavoring and coloring components.

19. The solid pharmaceutical dosage form of claim 14 wherein said orally administerable medicament is selected from the group consisting of analgesics, anti-inflammatories, antipyretics, antibiotics, antimicrobials, laxatives, anorexics, antihistamines, antiasthmatics, antidiuretics, antiflatuents, anti-emetics, antimigraine agents, antispasmodics, sedatives, antihyperactives, antihypertensives, tranquilizers, decongestants, and beta blockers.

20. The solid pharmaceutical dosage form of claim 14 wherein said orally administerable medicament is selected from the group consisting of peptides, proteins and oligonucleotides.

21. The solid pharmaceutical dosage form of claim 14 wherein said at least one saliva activated effervescent agent is present in an amount between about 20% by weight and 80% by weight.

REMARKS

The present application is a Continuation Application of U.S. Patent Application No. 09/327,814 filed June 8, 1999. The composition claims of the parent application were canceled during prosecution of the parent application, at which time, the parent application was limited to prosecution of the method claims. The purpose of this Continuation Application is to continue prosecution of the composition claims.

The composition claims were previously rejected under 35 U.S.C. § 102(b) as being anticipated by *Wehling et al.*, U.S. Patent No. 5,178,878. The composition claims were also previously rejected under 35 U.S.C. § 103(a) as being obvious over *Wehling et al.* in view of *Tsuk et al.*, U.S. Patent No. 3,972,995, *Roser et al.*, U.S. Patent No. 5,958,455, *Snipes*, U.S. Patent No. 5,135,752, and *Balkin*, U.S. Patent No. 5,656,284.

The Preliminary Amendment cancels all of the original claims and introduces new composition claims 14-21. Claims 14-21 differ from the original filed composition claims in that they include the limitation that the orally administerable medicament is not substantially encompassed by or dispersed in a material that prevents absorption of the medicament across the oral mucosa. Support for this recitation is found, *inter alia*, in the specification's teaching that the effervescent agent is used to promote absorption of the medicament across the oral mucosa. Thus, by definition, the claims necessarily cannot cover a composition in which the medicament is substantially surrounded by or dispersed in a material that prevents absorption of the medicament across the oral mucosa. No new matter has been added in the Preliminary Amendment and entry of these amendments is therefore respectively requested.

By amending the claims in this manner, claims 14-21 now patentably distinguish over *Wehling* alone or in combination with *Tusk, Roser, Snipes*, and *Balkin*. In particular, the primary reference *Wehling* teaches compositions and methods for administering said compositions in which the active ingredients are substantially encompassed by or dispersed in a

protective coating or matrix which shields the pharmaceutical ingredient from the environment of the mouth. (*See Wehling* at Col. 1, lns. 25-23.) The protective coating of *Wehling* is intended to prevent dissolution of the active ingredient in the mouth after the dosage form is rapidly disintegrated and before the contents are swallowed. Its object is therefore to prevent exposure and dissolution of the drug in the mouth. Drug has to be in solution for taste to be perceived and *Wehling* is primarily concerned with taste masking.

The claims have been amended to further distinguish the invention over *Wehling* on this point. In particular, the claims now recite that the dosage form has a medicament that is not substantially encompassed by or dispersed in a material that prevents absorption of the active ingredient across the oral mucosa.

The teachings of *Tusk*, *Roser*, *Snipes* and *Balkin* do not cure the deficiencies of *Wehling*. Although these secondary references teach holding the dosage forms identified in these references in the mouth, the secondary references do not provide any motivation for one skilled in the art to modify the compositions of *Wehling*, namely, by removing the protective coating or by replacing the protective coating with a coating that does not prevent exposure of the medicament in the mouth. Moreover, one skilled in the art would not be motivated even to combine the teachings of *Wehling* with the methods of the secondary references since *Wehling* teaches away from the administration of the active ingredient across the oral mucosa by preventing exposure of the active ingredient in the mouth.

In view of the above claim amendments and foregoing remarks, it is believed that this application is now in condition for allowance. Reconsideration is respectfully requested. However, if the Examiner still believes that there are any objections to this application, she is encouraged to telephone the undersigned at (908) 654-5000.

If there are any additional charges in connection with this Preliminary Amendment, the Examiner is authorized to charge Applicants' Deposit Account No. 12-1095.

Respectfully submitted,

LERNER, DAVID, LITTENBERG,
KRUMHOLZ & MENTLIK, LLP

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PATENT APPLICATION
CIMA 3.0-030 CONT II

SUBLINGUAL BUCCAL EFFERVESCENT

CROSS-REFERENCE TO RELATED APPLICATION

The present application is a continuation application of United States Patent Application No. 09/277,424 filed March 26, 1999.

BACKGROUND OF THE INVENTION

The present invention claims the benefit of the United States Provisional Application No. 60/079,652 filed on March 27, 1998, the disclosure of which is incorporated by reference herein.

FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions, and more particularly to pharmaceutical compositions for oral administration of a medicament, which contain an effervescent agent for enhancing oral drug absorption across the buccal, sublingual, and gingival mucosa.

DESCRIPTION OF PRIOR ART

Effervescents have been shown to be useful and advantageous for oral administration. *See* Pharmaceutical DosageForms: Tablets Volume I, Second Edition. A. Lieberman. ed. 1989, Marcel Dekker, Inc. As discussed in this text, and as commonly employed, an effervescent tablet is dissolved in water to provide a carbonated or sparkling liquid drink. *See* also U.S. Pat. Nos. 5,102,665 and 5,468,504 to Schaeffer, herein

incorporated by reference. In such a drink, the effervescent helps to mask the taste of medicaments.

Effervescent compositions have also been employed for use as taste masking agents in dosage forms which are not dissolved in water prior to administration. For example, U.S. Pat. No. 4,639,368 describes a chewing gum containing a medicament capable of absorption through the buccal cavity and containing a taste masking amount of an effervescent.

More recently effervescents have been employed to obtain rapid dissolution and/or dispersion of the medicament in the oral cavity. *See* U.S. Pat. Nos. 5,178,878 and 5,223,264. The effervescent tends to stimulate saliva production thereby providing additional water to aid in further effervescent action. These dosage forms give an agreeable presentation of the drug, particularly for patients who have difficulty in swallowing tablets or capsules. PCT application WO 97/06786 describes pre-gastric absorption of certain drugs using rapidly-disbursing dosage forms.

Various proposals have been advanced for oral mucosal administration of various drugs. When drugs are absorbed from the oral mucosa, they bypass the gastrointestinal and hepatic metabolism process. This can lead to a faster onset of action and/or improved bioavailability of a drug. However, many compounds do

not rapidly penetrate the oral mucosa. *See*, e.g., Christina Graffner, Clinical Experience with Novel Buccal and Sublingual Administration; NOVEL DRUG DELIVERY AND ITS THERAPEUTIC APPLICATION, edited by L.F. Prescott and W.S. Nimmo (1989); David Harris & Joseph R. Robinson, Drug Delivery via the Mucous Membranes of the Oral Cavity; JOURNAL OF PHARMACEUTICAL SCIENCES, Vol. 81 (Jan. 1992); Oral Mucosal Delivery, edited by M.J. Rathbone, which are herein incorporated by reference. The compounds which may be well absorbed per-orally (through the gastrointestinal tract) may not be well absorbed through the mucosa of the mouth because the oral mucosa is less permeable than the intestinal mucosa and it does not offer as big a surface area as the small intestine.

Despite these and other efforts toward increasing the permeation of medicaments across the oral mucosa, there have been unmet needs for improved methods of administrating medicaments across the oral mucosa.

SUMMARY OF THE INVENTION

The pharmaceutical compositions of the present invention comprise an orally administerable medicament in combination with an effervescent agent used as penetration enhancer to influence the permeability of the medicament across the buccal, sublingual, and gingival mucosa.

DETAILED DESCRIPTION OF THE INVENTION

One aspect of this invention is to use effervescent as penetration enhancers for influencing oral drug absorption. Effervescent agents can be used alone or in combination with other penetration enhancers, which leads to an increase in the rate and extent of absorption of an active drug. It is believed that such increase can rise from one or all of the following mechanisms:

1. reducing the mucosal layer thickness and/or viscosity;

2. tight junction alteration;

3. inducing a change in the cell membrane structure; and

4. increasing the hydrophobic environment within the cellular membrane.

The present dosage forms should include an amount of an effervescent agent effective to aid in penetration of the drug across the oral mucosa. Preferably, the effervescent is provided in an amount of between about 5% and about 95% by weight, based on the weight of the finished tablet, and more preferably in an amount of between about 30% and about 80% by weight. It is particularly preferred that sufficient effervescent material be provided such that the evolved gas is more

than about 5cm^3 but less than about 30cm^3, upon exposure of the tablet to an aqueous environment. However, the amount of effervescent agent must be optimized for each specific drug.

The term "effervescent agent" includes compounds which evolve gas. The preferred effervescent agents evolve gas by means of a chemical reaction which takes place upon exposure of the effervescent agent (an effervescent couple) to water and/or to saliva in the mouth. This reaction is most often the result of the reaction of a soluble acid source and a source of carbon dioxide such as an alkaline carbonate or bicarbonate. The reaction of these two general compounds produces carbon dioxide gas upon contact with water or saliva. Such water-activated materials must be kept in a generally anhydrous state and with little or no absorbed moisture or in a stable hydrated form, since exposure to water will prematurely disintegrate the tablet. The acid sources may be any which are safe for human consumption and may generally include food acids, acid and hydrite antacids such as, for example: citric, tartaric, amalic, fumeric, adipic, and succinics. Carbonate sources include dry solid carbonate and bicarbonate salt such as, preferably, sodium bicarbonate, sodium carbonate, potassium bicarbonate and potassium carbonate, magnesium carbonate and the like.

Reactants which evolve oxygen or other gasses and which are safe for human consumption are also included.

The effervescent agent(s) of the present invention is not always based upon a reaction which forms carbon dioxide. Reactants which evolve oxygen or other gasses which are safe for human consumption are also considered within the scope. Where the effervescent agent includes two mutually reactive components, such as an acid source and a carbonate source, it is preferred that both components react completely. Therefore, an equivalent ratio of components which provides for equal equivalents is preferred. For example, if the acid used is diprotic, then either twice the amount of a mono-reactive carbonate base, or an equal amount of a di-reactive base should be used for complete neutralization to be realized. However, in other embodiments of the present invention, the amount of either acid or carbonate source may exceed the amount of the other component. This may be useful to enhance taste and/or performance of a tablet containing an overage of either component. In this case, it is acceptable that the additional amount of either component may remain unreacted.

The present dosage forms may also include in amounts additional to that required for effervescence a pH adjusting substance. For drugs that are weakly

acidic or weakly basic, the pH of the aqueous environment can influence the relative concentrations of the ionized and unionized forms of the drug present in solution according to the Henderson-Hasselbach equation. The pH solutions in which an effervescent couple has dissolved is slightly acidic due to the evolution of carbon dioxide. The pH of the local environment, e.g., saliva in immediate contact with the tablet and any drug that may have dissolved from it, may be adjusted by incorporating in the tablet a pH adjusting substances which permit the relative portions of the ionized and unionized forms of the drug to be controlled. In this way, the present dosage forms can be optimized for each specific drug. If the unionized drug is known or suspected to be absorbed through the cell membrane (transcellular absorption) it would be preferable to alter the pH of the local environment (within the limits tolerable to the subject) to a level that favors the unionized form of the drug. Conversely, if the ionized form is more readily dissolved the local environment should favor ionization.

The aqueous solubility of the drug should preferably not be compromised by the effervescent and pH adjusting substance, such that the dosage forms permit a sufficient concentration of the drug to be present in the unionized form. The percentage of the pH adjusting

substance and/or effervescent should therefore be adjusted depending on the drug.

Suitable pH adjusting substance for use in the present invention include any weak acid or weak base in amounts additional to that required for the effervescence or, preferably, any buffer system that is not harmful to the oral mucosa. Suitable pH adjusting substance for use in the present invention include, but are not limited to, any of the acids or bases previously mentioned as effervescent compounds, disodium hydrogen phosphate, sodium dihydrogen phosphate and the equivalent potassium salt.

The active ingredient suitable for use in the present dosage forms can include systematically distributable pharmaceutical ingredients, vitamins, minerals, dietary supplements, as well as non-systematically distributable drugs. Preferably, the active ingredient is a systemically active pharmaceutical ingredient which is absorbable by the body through the oral mucosa. Although the dosage forms can be employed with a wide range of drugs, as discussed below, it is especially suitable for drugs and other pharmaceutical ingredients which suffer significant loss of activity in the lumen of the gastrointestinal tract or in the tissues of the gastrointestinal tract during absorption process or upon passage through the liver

after absorption in the intestinal tract. Absorption through the oral mucosa allows the drug to enter the systemic circulation without first passing through the liver, and thus alleviates the loss of activity upon passage through the liver.

Pharmaceutical ingredients may include, without limitation, analgesics, anti-inflammatories, antipyretics, antibiotics, antimicrobials, laxatives, anorexics, antihistamines, antiasthmatics, antidiuretics, antiflatuents, antimigraine agents, antispasmodics, sedatives, antihyperactives, antihypertensives, tranquilizers, decongestants, beta blockers; peptides, proteins, oligonucleotides and other substances of biological origin, and combinations thereof. Also encompassed by the terms "active ingredient(s)", "pharmaceutical ingredient(s)" and "active agents" are the drugs and pharmaceutically active ingredients described in *Mantelle*, U.S. Pat. No. 5,234,957, in columns 18 through 21. That text of *Mantelle* is hereby incorporated by reference. Alternatively or additionally, the active ingredient can include drugs and other pharmaceutical ingredients, vitamins, minerals and dietary supplements as the same are defined in U.S. Pat. No. 5,178,878, the disclosure of which is also incorporated by reference herein.

The dosage form preferably includes an effervescent couple, in combination with the other ingredients to enhance the absorption of the pharmaceutical ingredient across the oral mucosa and to improve the disintegration profile and the organoleptic properties of the dosage form. For example, the area of contact between the dosage form and the oral mucosa, and the residence time of the dosage form in the oral cavity can be improved by including a bioadhesive polymer in this drug delivery system. *See*, e.g., Mechanistic Studies on Effervescent-Induced Permeability Enhancement by Jonathan Eichman (1997), which is incorporated by reference herein. Effervescence, due to its mucus stripping properties, would also enhance the residence time of the bioadhesive, thereby increasing the residence time for the drug absorption. Non-limiting examples of bioadhesives used in the present invention include, for example, Carbopol 934 P, Na CMC, Methocel, Polycarbophil (Noveon AA-1), HPMC, Na alginate, Na Hyaluronate and other natural or synthetic bioadhesives.

In addition to the effervescence-producing agents, a dosage form according to the present invention may also include suitable non-effervescent disintegration agents. Non-limiting examples of non-effervescent disintegration agents include: microcrystalline, cellulose, croscarmelose sodium, crospovidone, starches,

corn starch, potato starch and modified starches thereof, sweeteners, clays, such as bentonite, alginates, gums such as agar, guar, locust bean, karaya, pecitin and tragacanth. Disintegrants may comprise up to about 20 weight percent and preferably between about 2 and about 10% of the total weight of the composition.

In addition to the particles in accordance with the present invention, the dosage forms may also include glidants, lubricants, binders, sweeteners, flavoring and coloring components. Any conventional sweetener or flavoring component may be used. Combinations of sweeteners, flavoring components, or sweeteners and flavoring components may likewise be used.

Examples of binders which can be used include acacia, tragacanth, gelatin, starch, cellulose materials such as methyl cellulose and sodium carboxy methyl cellulose, alginic acids and salts thereof, magnesium aluminum silicate, polyethylene glycol, guar gum, polysaccharide acids, bentonites, sugars, invert sugars and the like. Binders may be used in an amount of up to 60 weight percent and preferably about 10 to about 40 weight percent of the total composition.

Coloring agents may include titanium dioxide, and dyes suitable for food such as those known as F.D.&C. dyes and natural coloring agents such as grape skin extract, beet red powder, beta-carotene, annato,

carmine, turmeric, paprika, etc. The amount of coloring used may range from about 0.1 to about 3.5 weight percent of the total composition.

Flavors incorporated in the composition may be chosen from synthetic flavor oils and flavoring aromatics and/or natural oils, extracts from plants, leaves, flowers, fruits and so forth and combinations thereof. These may include cinnamon oil, oil of wintergreen, peppermint oils, clove oil, bay oil, anise oil, eucalyptus, thyme oil, cedar leave oil, oil of nutmeg, oil of sage, oil of bitter almonds and cassia oil. Also useful as flavors are vanilla, citrus oil, including lemon, orange, grape, lime and grapefruit, and fruit essences, including apple, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth. Flavors which have been found to be particularly useful include commercially available orange, grape, cherry and bubble gum flavors and mixtures thereof. The amount of flavoring may depend on a number of factors, including the organoleptic effect desired. Flavors may be present in an amount ranging from about 0.05 to about 3 percent by weight based upon the weight of the composition. Particularly preferred flavors are the grape and cherry flavors and citrus flavors such as orange.

One aspect of the invention provides a solid, oral tablet dosage form suitable for sublingual, buccal, and gingival administration. Excipient fillers can be used to facilitate tableting. The filler desirably will also assist in the rapid dissolution of the dosage form in the mouth. Non-limiting examples of suitable fillers include: mannitol, dextrose, lactose, sucrose, and calcium carbonate.

METHOD OF MANUFACTURE

Tablets can either be manufactured by direct compression, wet granulation or any other tablet manufacturing technique. *See*, e.g., U.S. Pat. Nos. 5,178,878 and 5,223,264, which are incorporated by reference herein. The tablet may be a layered tablet consisting of a layer of the active ingredient sandwiched between a bioadhesive layer and an effervescence layer. Other layered forms which include the ingredients set forth above in layers of diverse compositions.

Effervescence Level:	Between 5% - 95%
Tablet size:	Between 3/16" - 5/8"
Tablet hardness:	Between 5N and 80N
Route of administration:	Sublingual, Buccal, Gingival

The dosage form may be administered to a human or other mammalian subject by placing the dosage form in

the subject's mouth and holding it in the mouth, either adjacent a cheek (for buccal administration), beneath the tongue (for sublingual administration) and between the upper lip and gum (for gingival administration). The dosage form spontaneously begins to disintegrate due to the moisture in the mouth. The disintegration, and particularly the effervescence, stimulates additional salivation which further enhances disintegration.

EXAMPLE 1

The dosage form should include Fentanyl, an effervescent and pH adjusting substance so that the pH is adjusted to neutral (or slightly higher) since the pKa of fentanyl is 7.3. At this pH, the aqueous solubility of this poorly water-soluble drug would not be compromised unduly, and would permit a sufficient concentration of the drug to be present in the unionized form.

Two fentanyl formulations, each containing 36% effervescence, were produced. These tablets were compressed using half-inch shallow concave punches.

FORMULATION	COMPONENT	QUANTITY (MG)
SHORT	Fentanyl, citrate, USP	1.57
DISINTEGRATION	Lactose monohydrate	119.47
TIME	Microcrystalline Cellulose, Silicified	119.47
	Sodium carbonate, anhydrous	46.99
	Sodium bicarbonate	105
	Citric acid, anhydrous	75
	Polyvinylphrrolidone, cross-linked	25
	Magnesium stearate	5
	Colloidal silicon dioxide	2.5
	Total tablet mass	**500**
LONG	Fentanyl citrate, USP	1.57
DISINTEGRATION	Lactose monohydrate	270.93
TIME	Sodium carbonate, anhydrous	40.00
	Sodium bicarbonate	105
	Citric acid, anhydrous	75
	Magnesium stearate	5
	Colloidal silicon dioxide	2.5
	Total tablet mass	**500**

EXAMPLE 2

The dosage form included prochlorperazine (pKa=8.1), an effervescent and pH adjusting substance so that a slightly higher pH is produced to facilitate the permeation enhancement.

With respect to prochlorperazine, an anti-emetic drug, two formulations, buccal and sublingual, were developed. The buccal tablets were compressed as quarter inch diameter biconvex tablets, whereas the sublingual tablets were three-eighths inch diameter biconvex tablets. These dimensions were chosen to give a comfortable fit in the respective part of the oral cavity for which they were designed. The formulae for these tablets are as follows:

FORMULATION	COMPONENT NAME	QUANTITY (MG)
BUCCAL	Prochlorperazine	5.00
	Sodium Bicarbonate	15.52
	Citric Acid, Anhydrous	11.08
	Sodium Bicarbonate	45.78
	HPMC K4M Prem	5.00
	Dicalcium phosphate dihydrate	5.00
	Mannitol	11.67
	Magnesium Stearate	0.95
	Total	**100.00**
SUBLINGUAL	Prochlorperazine	5.00
	Sodium Bicarbonate	61.25
	Citric Acid, Anhydrous	43.75
	Sodium Bicarbonate	95
	Sodium carbonate	91.25
	HPMC Methocel K4M Prem	40
	Mannitol	60
	Magnesium Stearate	3.75
	Total	**400**

WE CLAIM

1. A solid pharmaceutical dosage form adapted for direct oral administration across the buccal, sublingual and gingival mucosa comprising:

at least one saliva activated effervescent agent and a pharmaceutically effective amount of an orally administerable medicament; wherein said at least one saliva activated effervescent increases absorption of said orally administerable medicament across the buccal, sublingual and gingival mucosa.

2. The solid pharmaceutical dosage form of claim 1 further comprising at least one pH adjusting substance.

3. The solid pharmaceutical dosage form of claim 1 further comprising a bioadhesive, wherein said bioadhesive increases the contact time between said dosage form and the oral cavity.

4. The solid pharmaceutical dosage form of claim 1 further comprising a non-effervescent disintegration agent.

5. The solid dosage pharmaceutical dosage form of claim 1 further comprising glidants, lubricants, binders, sweeteners, flavoring and coloring components.

6. The solid dosage pharmaceutical dosage form of claim 1 wherein said orally administerable medicament is selected from the group consisting of

analgesics, anti-inflamatories, antipyretics, antibiotics, antimicrobials, laxatives, anorexics, antihistamines, anitasthmatics, antidiuretics, anitflatuents, anti-emtics, antimigrane agents, antispasmodics, sedatives, antihyperactives, antihypertensives, tranquilizers, decongestants, and beta blockers.

7. The solid dosage pharmaceutical dosage form of claim 1 wherein said orally administerable medicament is selected from the group consisting of peptides, proteins and oligonucleotides.

8. The solid dosage pharmaceutical dosage form of claim 1 wherein said at least one saliva activated effervescent agent is present in an amount between about 20% by weight and 80% by weight.

9. A method of administering at least one systemically distributable pharmaceutical agent comprising:

a) providing a tablet including at least one effervescent agent and a pharmaceutically effective amount of an orally administerable medicament;

b) placing said tablet in the mouth of a patient so that saliva in said patients mouth activates said at least one effervescent agent in said tablet, whereby said at least one effervescent promotes absorption of

said orally administerable medicament across the oral mucosa.

10. The method according to claim 9 wherein said tablet further includes at least one pH adjusting substance.

11. The method of administering the tablet according to claim 9 further comprising the step of holding said tablet in said mouth adjacent a cheek for buccal administration.

12. The method of administering the tablet according to claim 9 further comprising the step of holding said tablet in said mouth beneath the tongue for sublingual administration.

13. The method of administering the tablet according to claim 9 further comprising the step of holding said tablet in said mouth between the upper lip and gum for gingival administration.

ABSTRACT

A pharmaceutical dosage form adapted to supply a medicament to the oral cavity for buccal, sublingual or gingival absorption of the medicament which contains an orally administerable medicament in combination with an effervescent for use in promoting absorption of the medicament in the oral cavity. The use of an additional pH adjusting substance in combination with the effervescent for promoting the absorption drugs is also disclosed.

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

ATTORNEY'S DOCKET NO.: CIMA 3.0-030 CONT

As a below-named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name;
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

SUBLINGUAL BUCCAL EFFERVESCENT the specification of which

☐ is attached hereto

☒ was filed on June 8, 1999 as United States Application Number or PCT International Application Number 09/327,814 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) of any foreign application(s) for patent or inventor's certificate or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate, or any PCT international application having a filing date before that of the application on which priority is claimed:

PRIOR FOREIGN APPLICATION(S)			
COUNTRY	APPLICATION NUMBER	DATE OF FILING (month, day, year)	PRIORITY CLAIMED
			YES ☐ NO ☐
			YES ☐ NO ☐
			YES ☐ NO ☐
LISTING OF FOREIGN APPLICATIONS CONTINUED ON PAGE 3 HEREOF ☐ YES ☒ NO			

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below:

Application Number: 60/079,652 Filing Date: March 27, 1998

Application Number: Filing Date:

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

U.S. Parent Application Serial Number: 09/277,424 Parent Filing Date: March 26, 1999 Parent Patent No.:

U.S. Parent Application Serial Number: Parent Filing Date: Parent Patent No.:

PCT Parent Number: Parent Filing Date:

LISTING OF US APPLICATIONS CONTINUED ON PAGE 3 HEREOF: ☐ YES ☒ NO

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

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DECLARATION -- Page 2

ATTORNEY DOCKET NO. CIMA 3.0-030 CONT

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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☐ Additional inventors are being named on separately numbered sheets attached hereto.